Lack of association between ankylosing spondylitis and a functional polymorphism of *PTPN22* proposed as a general susceptibility marker for autoimmunity.

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*Short running title: PTPN22 polymorphism in AS.*

*Keywords:* ankylosing spondylitis, *PTPN22* gene, polymorphism, susceptibility.
Ankylosing spondylitis (AS) is a common chronic rheumatic disease whose etiology arises as a result of the contribution of environmental factors and a strong genetic component.[1] One crucial point in the pathogenesis of the disease is the regulation of T-cell response.[2] Recently, the functional 1858 C/T polymorphism of \textit{PTPN22}, the gene that encodes a lymphoid-specific protein tyrosine phosphatase (LYP), has been shown to be associated with several autoimmune diseases (ADs), supporting the hypothesis that common etiopathological pathways are shared by different autoimmune diseases. [3] LYP plays a key role as a negative regulator of T-cell activation. [4] It seems that the SNP 1858 C/T disrupts the interaction between LYP and Csk, probably leading to an over-activated T-cell response.[5]

Taking into account the functional relevance of the \textit{PTPN22} 1858 C/T polymorphism, and its association with a wide range of ADs, the aim of this study was to investigate for the first time the possible implication of the SNP with regard to susceptibility to AS. A total of 197 AS patients meeting the modified New York criteria for AS [6] were recruited from Hospital Virgen de las Nieves (Granada, Spain) and Hospital Xeral-Calde (Lugo, Spain). A total of 551 blood bank donors and bone marrow donors were included as healthy controls. All the subjects were of white Spanish origin. Samples were genotyped for \textit{PTPN22} 1858C→T variants as previously described. [7] Statistical analysis to compare allelic and genotypic distributions was performed by \(\chi^2\) test using Statcalc program (Epi Info 2002; Centers for Disease Control and Prevention, Atlanta, GA, USA).

We did not observe any statistically significant differences after comparing allele and genotypic frequencies of \textit{PTPN22} 1858C→T between AS patients and controls (Table 1).

Table 1.- Allele and genotype frequencies of the \textit{PTPN22} 1858C→T polymorphism in AS patients and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>AS patients (%)</th>
<th>Healthy controls (%)</th>
<th>P value*</th>
<th>OR (95% CI)</th>
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<tr>
<td></td>
<td>n= 197</td>
<td>n= 551</td>
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<td>C/C</td>
<td>166 (84.3)</td>
<td>462 (83.8)</td>
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<td>3 (1.5)</td>
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|          |          |          |          |             |
| C        | 360 (91.4) | 1008 (91.5) | 0.95     | 0.99 (0.64-1.52)  |
| T        | 34 (8.6)  | 94 (8.5)  | 0.95     | 1.01 (0.66-1.55)  |

* 3x2 contingency table, overall \(P\) value= 0.73

In addition, comparison of genotypes carrying T allele (CT+TT vs CC) between AS patients and controls did not reach statistically significant skewing. Similarly, no statistically significant differences were found when we stratified AS patients with regard to HLA-B27 status (data not shown).

The lack of association that we show here could be due to a false negative, given our underpowered sample size. Due to this, we cannot completely exclude a weak effect of this polymorphism in AS and further investigations in different populations are required. Recent studies of the \textit{PTPN22} 1858C/T polymorphism have reported a lack of association with some ADs. [8] The lack of association with these ADs may indicate a common etiological mechanism that is different from the associated ADs. It has been proposed that the susceptibility of the polymorphism may predispose individuals to autoimmunity by promoting the generation of autoantibodies that contribute to disease onset and progression [9]. The existence of humoral abnormalities in PTPN22-knockout
mice strengthens the hypothesis that autoantibody production is a prominent feature of the ADs that are associated with PTPN22.[10] Based on that, the lack of autoantibody production in AS might explain the negative association between PTPN22 1858C/T polymorphism and this condition.

In conclusion, the lack of association of PTPN22 underlies that susceptibility factors for AD are not shared among all ADs.
ACKNOWLEDGMENTS
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CONFLICT OF INTEREST STATEMENT
No Conflict of Interest has been declared by the authors.

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